REMARKS

I. Amendments

Claims 1-7, 9 and 11-16 have been withdrawn, claims 8 and 10 have been amended, and claim 17 has been added. Upon entry of the amendment, claims 8, 10 and 17 will be pending. The amendment does not constitute new matter and is supported throughout the specification, for example, in Example 1.

II. Rejections

Rejections under 35 U.S.C. § 101

Claims 8 and 10 stand rejected as the claimed invention allegedly is not supported by either a specific or substantial asserted utility or a well-established utility. The claims are drawn to a transgenic mouse whose genome comprises a heterozygous disruption in a Cerl gene comprising SEQ ID NO: 1, wherein as a result of the disruption, the mouse has increased anxiety. The Examiner essentially argues that: (i) studying the mouse to determine the function of a gene is not in and of itself a substantial utility (page 2); and (ii) none of the phenotypes correlate to a useful phenotype because the phenotypes described are not specific to a disease and are not linked to a disruption in the human equivalent of SQ ID NO:1 (pages 3-4).

Applicant respectfully disagrees.

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has either a well-established utility or is useful for a particular practical purpose. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined. According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
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> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834) (emphasis added). Thus, the knockout mouse has been accepted as by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Applicant respectfully submits that this is not a case where the sole asserted utility is as an object of use-testing (*See*, *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966);

"We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product"). The dicta in *Brenner* related to the patentability of a chemical compound which itself had no known use. The Court opined that the utility could not solely consist of testing the compound in order to determine a utility for the compound itself. In contrast, the mCAR2 knockout mouse is useful for the study of the utility and function of the mCAR2 gene, and not for the purpose of establishing a utility for the mouse. The practical distinction is clear: one skilled in the art would not understand what to do with a compound without a defined use, but would immediately recognize the use of a knockout mouse having a specific gene disruption.

Knockout mice may be appropriately analogized to other research tools, with respect to which the Patent Office has commented:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). The use of knockout mice as research tools is recognized by those skilled in the art. For example, according to Crabbe *et al.* (Science (1999) 284:1670-1672) *a reference cited by the Examiner*), "[t]argeted and chemically induced mutations in mice are valuable tools in biomedical research." As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

Finally, Applicant notes that in an Office Action dated December 19, 2002, the Examiner rejected the claimed invention as obvious under section 103. The Examiner argued: "[o]ne of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to determine the physiological role of a gene of interest by generation of a knockout mouse". (paper no. 12, page 11). Thus, while the Examiner argued that one skilled in the art would have been motivated to make the Applicant's claimed mouse, he also argues that one skilled in the art would not know how to use such a mouse once created. Applicant submits that the Examiner's previous statements are an admission that the present invention has a well-established utility, i.e., determining the function of a gene.

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice, i.e., increased anxiety. Utility of the claimed knockout mouse would be apparent to, and considered credible by, one of skill in the art, as the role of knockout mice in studying the anxiety is both specific and substantial.

The claimed knockout mouse demonstrates a role for the target gene in anxiety disorders. Therefore, the target gene correlates with a specific disorder. Anxiety disorders are a well-recognized condition which are the subject of drug development studies and treatment strategies. For example, there are currently in excess of sixty (60) clinical trials enrolling patients for the study of anxiety disorders (http://clinicaltrials.gov/ct/screen/BrowseAny?path=%2Fbrowse%2Fby-condition%2Faz%2FA%2FD001008%2BAnxiety%2BDisorders&recruiting=true). The broad interest in studying treatments for anxiety disorders establishes that the phenotype and the disease/disorder are one and the same. Further establishment of a correlation between the phenotype and the disease/disorder is unnecessary and unwarranted.

In addition, the utility of a knockout mouse demonstrating increased anxiety has been recognized as a useful tool in the discovery of anxiolytics. For example, Mombereau *et al.*

(*Neuropsychopharmacology* (2004) 29, 1050-62) discloses a $GABA_B$ receptor knockout having increased anxiety:

> Recently, we demonstrated that mice lacking the GABA(B(1)) subunit were more anxious than wild-type animals in several behavioural paradigms, most notably in the light-dark test. In an attempt to assess the effects of classical benzodiazepine anxiolytics on anxiety-like behaviour observed in these mice, animals were administered either chlordiazepoxide (10 mg/kg, p.o.) or diazepam (7.5 mg/kg, p.o.) prior to testing in the light-dark box. Surprisingly, in contrast with the wild-type mice, neither benzodiazepines decreased anxiety-like behaviour in GABA(B(1))(-/-) mice. These data suggest that targeted deletion of GABA(B(1)) subunit alters GABA(A) receptor function in vivo.

(abstract)(emphasis added)(http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15321743). Based on observations in the knockout mouse and subsequent pharmacological experiments using receptor antagonists, the authors proposed that the $GABA_B$ receptor serve as a novel therapeutic strategy for the development of anxiolytics.

In another example, Lewejohann et al., (*Behav Brain Res.* (2004) 23;154(1):273-89) observed increased anxiety in BC1 deficient mice:

> BC1 RNA is a small non-messenger RNA common in dendritic microdomains of neurons in rodents. In order to investigate its possible role in learning and behaviour, we compared controls and knockout mice from three independent founder lines established from separate embryonic stem cells. Mutant mice were healthy with normal brain morphology and appeared to have no neurological deficits. A series of tests for exploration and spatial memory was carried out in three different laboratories. The tests were chosen as to ensure that different aspects of spatial memory and exploration could be separated and that possible effects of confounding variables could be minimised. Exploration was studied in a barrier test, in an open-field test, and in an elevated plus-maze test. Spatial memory was investigated in a Barnes maze and in a Morris water maze (memory for a single location), in a multiple T-maze and in a complex alley maze (route learning), and in a radial maze (working memory). In addition to these laboratory tasks, exploratory behaviour and spatial memory were assessed under semi-naturalistic conditions in a large outdoor pen. The combined results indicate that BC1 RNA-deficient animals show behavioural changes best interpreted in terms of reduced exploration and increased anxiety. In contrast, spatial memory was not affected. In the outdoor pen, the survival rates of BC1-depleted mice were lower than in controls. Thus, we conclude that the neuron-specific non-messenger BC1 RNA contributes to the aptive modulation of behaviour.

(abstract)(emphasis added)(
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15302134).

In yet a further example, Haller et al. (*Behav Pharmacol.* (2004) 15(4):299-304) compared the effect of agents on CB1 deficient mice with wild-type controls:

> Cannabinoids are known to modulate GABAergic and glutamatergic transmission in cortical areas, the former via CB1 and the latter via a novel receptor. Pharmacological data demonstrate that several widely used cannabinoid ligands bind to both receptors, which may explain the inconsistencies in their behavioural effects. Earlier we showed that the cannabinoid antagonist SR-141716A affected behaviour in both CB1 knockout and wild-type animals, and its effect (anxiolysis) was different from that of CB1 gene disruption (anxiogenesis). In the present experiments, we studied the effects of the CB1 antagonist AM-251, and the cannabinoid agonist WIN-55,212-2 in wild-type as well as in CB1 knockout mice. CB1 knockout mice showed higher scores of anxiety-like behaviour than the wild-type animals in the elevated plus-maze. Selective blockade of CB1 receptors by AM-251 (0.3, 1 and 3 mg/kg) increased anxiety-like behaviour dose-dependently in the wild-type mice but had no effect in the knockouts. In wild types, the cannabinoid agonist WIN-55,212-2 (1 and 3 mg/kg) caused a decrease in anxiety-like behaviour, which was abolished by the CB1-selective antagonist AM-251 (3 mg/kg). The same agonist did not change plus-maze behaviour in CB1 knockout animals. These data demonstrate at the behavioural level that AM-251 and, at low concentrations, WIN-55,212-2, are selective ligands of the CB1 cannabinoid receptor in mice. Our studies on the behavioural effects of the cannabinoid antagonist SR-141716A and the CB1 antagonist AM-251 show that the CB1 and the novel cannabinoid receptor mediate anxiolytic and anxiogenic effects, respectively. This suggests that agonists of the former, or antagonists of the latter, are promising new compounds in the pharmacotherapy of anxiety.

(abstract)(emphasis added)(
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15252281). The above-cited references clearly demonstrate that one skilled in the art recognizes the utility of transgenic mice demonstrating anxiety related phenotypes, including in drug development studies.

The Examiner argues that the Applicant has not established a link between the recited phenotypes and the gene in humans. The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be

effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proferred by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, *citing In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo*

murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. As discussed above, the knockout mice have demonstrated increased anxiety. The acceptance among those of skill in the art of knockout mice demonstrating increased anxiety is clearly demonstrated by, for example, the above cited references.

That the specification may not disclose a link between these particular phenotypes and the gene in mice and humans is irrelevant to whether the claimed invention satisfies the utility requirement. In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption in a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied his initial burden.

It is respectfully submitted that the Examiner needs to assess utility in light of the nature of the invention. Applicant is claiming a knockout mouse. The burden should not be placed on Applicant to establish that mutations in the human homolog of the Cer1 gene result in the same phenotypes observed in mice. This task is more appropriately placed on the commercial and academic entities conducting further research using the present invention. As noted by the Federal Circuit, usefulness in patent law necessarily includes the expectation of further research and development. (*In re Brana* at 1442).

The Examiner also questions the veracity of the conclusions reached by Applicant with respect to the phenotypic data. The Examiner states that one of ordinary skill would have been critical of the data in the specification. Applicant submits that all of the pathological, physiological and behavioral observations and conclusions based thereon which are set forth in the specification were made by highly skilled pathologists and behavioral specialists. The conclusion that the claimed mice exhibit increased anxiety is based on observations of a decrease in average velocity during episodes of movement, decrease in total distance traveled, and an increase in the number of fecal boli. Applicant's conclusions are reasonable. It is also submitted that the Examiner is misreading the data table: the number of mice is set forth under the "count" column. Comparison of rows 1 and 3 of Table 1, where 10 homozygous mice were compared with 10 control mice, reveals a statistically significant decrease in total travel.

The Examiner further argues that the specification does not teach the age, gender or strain of the control mice. All of the comparative studies were performed as one of skill in the art would expect them to have been performed: using age, gender and strain matched control mice. Recitation in the specification is not necessary to support the Applicant's conclusions.

In summary, Applicant submits that the claimed Cer1 gene knockout mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the Cer1 gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the specific phenotypes of the transgenic mice demonstrate that the mice are useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107). Withdrawal of the rejections under section 101 is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 8 and 10 because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility

rejection. Applicants respectfully traverse the rejection. For the reasons set forth above, the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the invention. Applicant respectfully requests withdrawal of the rejection.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-67.

Respectfully submitted,

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